Cyclocarbonylative Sonogashira Reactions of 1-Ethynylbenzyl Alcohols: Synthesis of 1-Carbonylmethylene-1,3-Dihydroisobenzofurans

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Abstract: In this work we present a carbonylative Sonogashira reaction of *o*-ethynyl benzylalcohols and aryl iodides, followed by a cyclization process to afford selectively carbonylmethylene isobenzofurans in high yields and in an atom-economic fashion. The reaction can be performed in the absence of CuI, with a small amount of $PdCl_2(PPh_3)_2$ (0.2–0.5 mol%) using aryl iodides bearing both electron withdrawing and electron donating groups. Between the two possible stereoisomers, (*Z*)-isobenzofurans derivatives are obtained as major products but, when the reaction is extended to a secondary alcohol, an interesting switch in the stereoselectivity is observed.

Introduction

The 1,3-dihydroisobenzofuran (phthalan) nucleus [Figure 1] is found in a vast class of natural and synthetic compounds displaying antimycotic, antibacteric,[1] antioxidant,[2], antihistaminic[3] and antitumoral[4] activity.

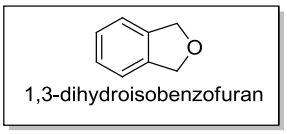
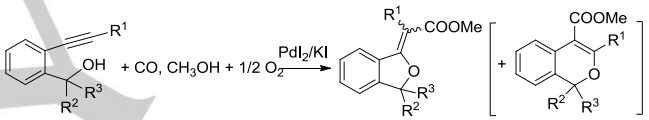


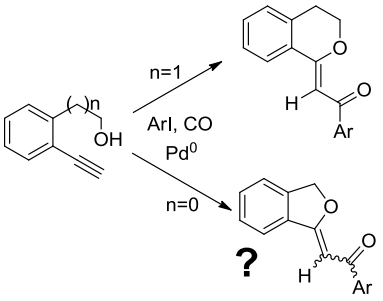
Figure 1. 1,3-Dihydroisobenzofuran structure.

Moreover, some synthetic analogues such as 3-alkylidene-1,3-dihydroisobenzofurans have been recently tested as free radical scavengers[5] and have been evaluated as antidepressant molecules[6] resulting to be more active than citalopram[7], the reference drug commonly used to treat depression.
Alkylidenephthalans are also endowed with a rich reactivity that makes them a versatile building block for the synthesis of functionalized phenanthrofurans[8], isoquinolinones[9] and spiroketals.[10]
Several methods for the preparation of 3-alkylidene-1,3-dihydroisobenzofurans are described in the literature. They are generally based on the cyclization of functionalized substrates such as alkynyloxiranes,[11] o-alkynylbenzaldehydes[12] and o-alkynylbenzyl alcohols often prepared via Sonogashira coupling of iodobenzyl alcohol and terminal acetylenes. In particular, intramolecular cyclization of alkynylalcohols can be promoted by a base (NaH,[13], KOH[14], ^{t}BuOK[15]) or mediated by lanthanide,[16] copper[17] and palladium[18] catalysts. In this field, Gabriele and co-workers[19] have developed an interesting approach based on the use of a PdI_2/KI system. In particular, by means of a palladium-catalyzed oxidative carbonylation reaction they obtained[20] alkoxycarbonylmethylene phthalans in good yields, together with small amounts of the corresponding benzopyrans compounds (Scheme 1).



Scheme 1. Synthesis of alkoxycarbonylmethylene-(1,3)-dihydroisobenzofurans by oxidative carbonylation of alkynylalcohols

Intrigued by this data and prompted by our recent results[21] on the Sonogashira cyclocarbonylative reaction of 2-(2-ethynylphenyl)ethanol which generated 2-alkylidene isochromans in high yields and stereoselectivity (Scheme 2, n = 1), we decided to investigate the application of this protocol to ethynylbenzylalcohol (Scheme 2, n = 0) in order to verify if the synthesis of carbonylmethylene-1,3-dihydroisobenzofurans could be achieved.



Scheme 2. Sonogashira cyclocarbonylative reaction of ethynyl alcohols

Results and Discussion

We started our investigation using equimolar amount of (2-ethynylphenyl)methanol **1a**, a commercial reactant, and iodobenzene (**2a**) as the coupling partner, employing the

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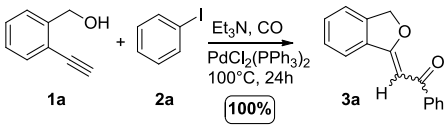
experimental conditions already optimized for the formation of isochromans.[21] Indeed, the reactions were performed under CO pressure (2.0 MPa) in Et_3N as both the solvent and the base, at 100°C and using $PdCl_2(PPh_3)_2$ (0.2 mol-%) as the catalyst. After 24 h, the reaction displayed the quantitative consumption of the precursors and the formation of 5-membered dihydroisobenzofuran **3a** as the sole product (Scheme 3).



Scheme 3. Preliminary Sonogashira cyclocarbonylative reaction between (2-ethynylphenyl)methanol and iodobenzene

Even if both 5-*exo-Dig* and *6-endo-Dig* derivatives could have been obtained according to Baldwin's rules[22], it is noteworthy that no traces of the possible benzopyran derivative were detected (Scheme 3).

Both stereoisomers *Z* and *E* of phthalan **3a** were present in the crude product but they were well distinguished through ^{1}H-NMR analysis. Indeed, according to the literature,[12a] proton $\mathbf{H_a}$ of the *E*-isomer, was found at unusually high chemical shift (9.43 ppm) due to its interaction with the carbonyl deshielding cone, while proton $\mathbf{H_b}$ appeared at higher field (7.75 ppm) (Figure 2).

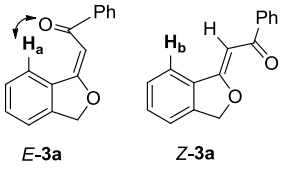
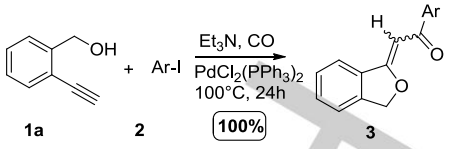


Figure 2. Stereoisomers *E/Z* of 2-(isobenzofuran-1(3H)-ylidene)-1-phenylethanone

Anyway, the two stereoisomers can be easily separated and isolated in a chemically pure form by column chromatography. Unexpectedly the relative amount of the two isomers changed after separation: *Z/E* crude: 63/37, pure: 68/25, suggesting a stereomutation of *E*-**3a** into *Z*-**3a** under purification conditions.

The same trend was observed when the reaction was extended to several iodoarenes possessing electron-donating and electron-withdrawing substituents in the *ortho* and *para* position (Scheme 4). As described in Table 1 in almost all the cases (entries 1-7) the reactions yielded the dihydroisobenzofurans **3** quantitatively. The *E*-derivative was always the minor product and an increasing of the *Z* compound was generally observed after purification. In order to evaluate if the interaction of the crude product with the stationary phase (SiO_2) or with the eluent ($CHCl_3$) could be the reason of the change in the ratio between the two isomers, 100 mg of pure *E*-**3f** were treated with SiO_2 in $CDCl_3$. After 24 h both the two steroisomers were present in reaction mixture and a *Z/E* ratio of 92/8 was observed which remained constant even after 5 more days (Scheme 5).



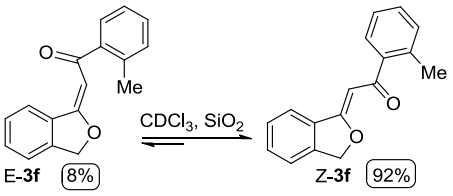
Scheme 4. Sonogashira cyclocarbonylative reactions between (2-ethynylphenyl)methanol and aryl iodides

Table 1. Cyclocarbonylative reactions of 2-(2-ethynylphenyl)ethanol and aryl iodides

Entry[a]	2	Ar	3	*Z* (%)[b]	*E* (%)[b]
1	**a**	Ph	**a**	63(68)	37(25)
2	**b**	1-Naphthyl	**b**	86(87)	14(10)
3	**c**	4-$MeOC_6H_4$	**c**	75(83)	25(14)
4	**d**	2-$MeOC_6H_4$	**d**	81(81)	19(14)
5	**e**	4-MeC_6H_4	**e**	59(60)	41(33)
6	**f**	2-MeC_6H_4	**f**	71(72)	29(27)
7	**g**	4-Cl	**g**	61(51)	39(11)
8[c]	**h**	2-NCC_6H_4	**h**	83(69)	/
9[d]	**i**	4-NCC_6H_4	**i**	50(33)	25(13)

[a] The reactions were performed with 2 mmol of **1a**, 2 mmol of **2**, 0.004 mmol di $PdCl_2(PPh_3)_2$ (0.2 mol-%), in 5 mL of Et_3N, at 100 °C, for 24 h, under CO (2.0 MPa). Conversions (100% in all the cases) were evaluated through GC and ^{1}H-NMR analysis. [b] Selectivity were evaluated through ^{1}H-NMR; in parentheses isolated yields are reported (the products were obtained chemically pure after column chromatography). [c] The reaction yielded also 17% 2-(3-(2-(hydroxymethyl)phenyl)propioloyl)benzonitrile **4**. [d] The reaction was performed in a 5mL Et_3N / 4 mL toluene mixture in order to dissolve **2;** 4-(3-(2-(hydroxymethyl)phenyl)propioloyl)benzonitrile **5** (25%) was also formed.

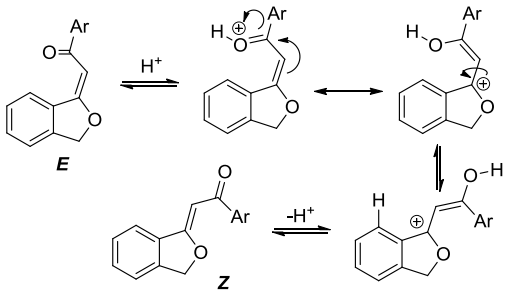
This means that *Z*-**3f** is more stable than the *E*-isomer by about 1.3 Kcal/mol[23] and this value is comparable with that reported for similar acylylidene isobenzofurans[12]. Probably, the presence of acidic traces during the purification step could cause the interconversion observed, as already pointed out by Herndon and co-workers[12a] (Scheme 6).



Scheme 5. Interconversion between the two stereoisomers

When the Sonogashira cyclocarbonylative reaction was carried out employing benzonitriles **2h** and **2i** (Table 1, entries 8 and 9), relevant amounts of 2-(3-(2-(hydroxymethyl)phenyl)propioloyl) benzonitrile **4** (17%) and 4-(3-(2-

(hydroxymethyl)phenyl)propioloyl) benzonitrile **5** (25%) were generated (Figure 3).



Scheme 6. Mechanism of stereomutation of *E*-**3a** into *Z*-**3a**

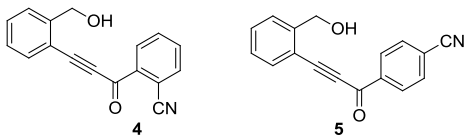
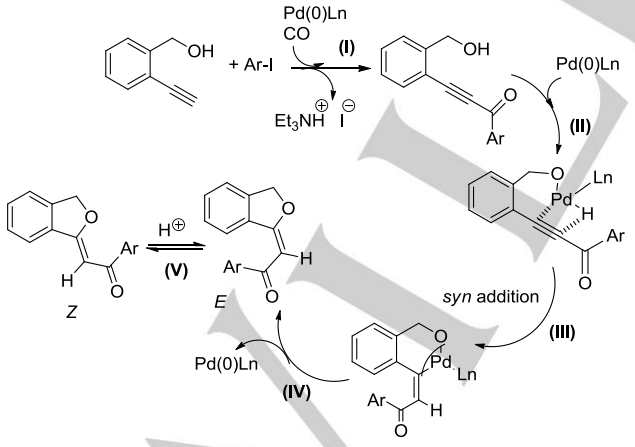


Figure 3. Carbonylative Sonogashira by-products

In order to rationalize all these outcomes, we propose the hypothetical mechanism depicted in Scheme 7. It involves first of all a carbonylative Sonogashira coupling between the iodo-derivative and the alkynyl moiety (Scheme 7, I); then a Pd(0) insertion into the O–H bond follows (Scheme 7, II) and a palladium hydride species is obtained. Subsequently, such species undergoes a *syn* hydropalladation step to the triple bond (Scheme 7, III). The following reductive elimination (Scheme 7, IV) regenerates Pd(0), affording isobenzofuran *E*-**3**, which equilibrates with the corresponding *Z*-**3** isomer (Scheme 7, V).

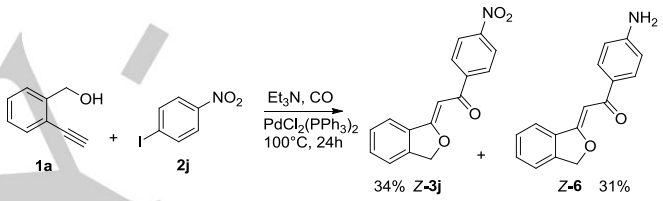


Scheme 7. Hypothesis of mechanism

The formation of the two stereoisomers *E* and *Z* is apparently in contrast to the data obtained in our previous work on the synthesis of isobenzopyrans through the Sonogashira cyclocarbonylation reaction of 2-(2-ethynylphenyl)ethanol[21]. Indeed in that case, not even traces of the *E* species were detected. In the light of the recent results, our prior data could be explained with a trans hydropalladation step to the triple bond of the alkynyl ketone intermediate or, more probably, with a very fast conversion of the *E* isomer into the *Z* one as soon as it is formed in the reaction medium.

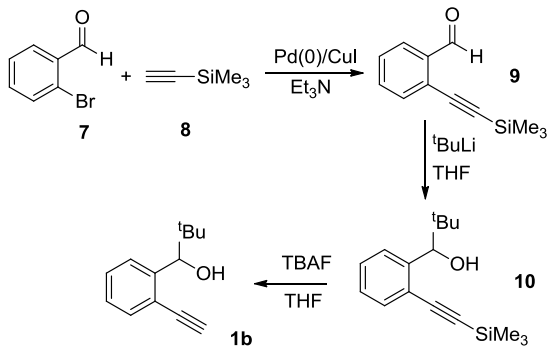
The proposed mechanism is also consistent with the presence of uncyclized products obtained when using iodobenzonitriles as the coupling partners (Table 1, entries 8 and 9,). In fact, in this case, the presence of a strong electron-withdrawing group could reduce the electronic density on the triple bond of the Sonogashira coupling product, thus slowing the hydropalladation step.

The presence of palladium-H species during the catalytic cycle could be the reason of the formation of (*Z*)-1-(4-aminophenyl)-2-(isobenzofuran-1(3H)-ylidene)ethanone **6** in the reaction between 1-iodo-4-nitrobenzene **2j** and **1a** (Scheme 8). Indeed, the aminobenzofuran **6** could be reasonably derived from the reduction of the NO_2 moiety into NH_2, as already observed in our previous work on the synthesis of isochromans.[21].



Scheme 8. Sonogashira cyclocarbonylative reactions between (2-ethynylphenyl)methanol and 1-iodo-4-nitrobenzene

Finally, the Sonogashira cyclocarbonylative reaction was extended to a sterically hindered secondary alcohol. We chose tert-butyl alcohol **1b** as a representative example. Since it is not commercially available, **1b** was synthesized starting from aldehyde **7**, according to the procedure (not optimized) described in Scheme 9.[14]

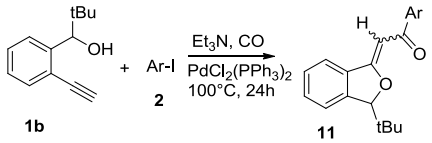


Scheme 9. Preparation of 1-(2-ethynylphenyl)-2,2-dimethylpropan-1-ol

2-Bromobenzaldehyde was initially coupled with trimethylsilylacetylene to yield product **9** (87%). ^{t}BuLi was then added to 2-(trimethylsilylethynyl)benzaldehyde, generating 2,2-

dimethyl-1-(2-((trimethylsilyl)ethynyl)phenyl)propan-1-ol **10** (28%). Finally the $SiMe_3$ group was easily removed by treatment of **10** with an excess amount of tetrabutylammonium fluoride (TBAF, 77%).

A preliminary study on the carbocyclization reactions (Scheme 10, Table 2) showed again a quantitative conversion of the reagents but a slightly higher catalytic load (0.5 mol-%) was necessary to get the desired products (Table 2, entries 1 vs 2). To our surprise, we observed that, at least in the few cases examinated, when the hindered alcohol **1b** was employed with iodoarenes **2a,d,** the stereoselectivity of the process was higher towards the *E*-isomer (Table 2, entries 2 and 3).



Scheme 10. Cyclocarbonylative Sonogashira reactions of 1-(2-ethynylphenyl)-2,2-dimethylpropan-1-ol

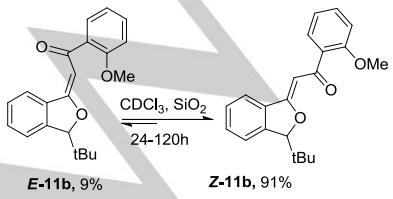
Table 2. Cyclocarbonylative reactions of 1-(2-ethynylphenyl)-2,2-dimethylpropan-1-ol and aryl iodides

Entry[a]	2	Ar	Cat. (%)	Conv.[b] (%)	11	*Z* (%)[b]	*E* (%)[b]
1	**a**	Ph	**0.2**	**28**	**a**	26	74
2	**a**	Ph	**0.5**	**100**	**a**	22(15)	78(57)
3	**d**	2-$MeOC_6H_4$	**0.5**	**100**	**b**	44(32)	56(35)

[a] The reactions were performed with 2 mmol of **1a**, 2 mmol of **2**, in 5 mL of Et_3N, at 100 °C, for 24 h, under CO (2.0 MPa). [b] Conversions were evaluated through ^{1}H-NMR analysis; in parentheses isolated yields are reported.

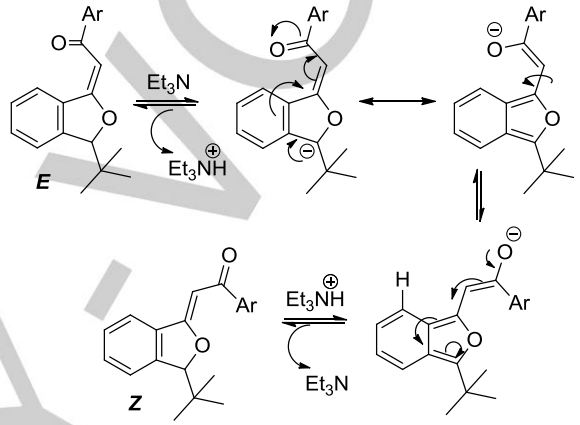
These results could be tentatively ascribed to a reduced rate of all the catalytic cycle due to the higher steric hindrance of substrate **1b** respect to **1a**; thus a less conversion of isomer ***E*** into ***Z*** (Scheme 7 step **V**) resulted. Indeed a greater amount of catalyst had to be used in order to obtain a complete conversion of the reagents (Table 2, entries 1 and 2).

Anyway, when a sample of pure ***E*-11b** was let equilibrate in $CDCl_3$ and the mixture content was monitored, after 24 hours, a *Z/E* ratio of 91:9 was detected and it remained constant after several days (Scheme 11), clearly confirming that the *Z* isomer is thermodynamically the more stable one.



Scheme 11. Stereomutation between ***E*-11b** and ***Z*-11c**

The difference in the stereoisomers ratio observed at the end of the reaction (Table 2, entry 3, 44:56) respect to the one detected after the steromutation test (Scheme 11, 91:1) could be due to the experimental conditions used in the two cases. Indeed, while the interconversion of pure *E* into the *E/Z* mixture is performed under acid conditions, the cyclocarbonylation reactions are carried out in Et_3N. As depicted in Scheme 12, in the second case the isomerization requires an extraction of a proton from the substituted carbon atom by triethylamine. In the case of alcohol **1b** the very hindered tert-butyl moiety would interfere with the approach of the base slowing down all the isomerization process (Scheme 12).



Scheme 12. Possible mechanism of stereomutation under basic reaction conditions

Finally, two reactions have been performed using benzoylchloride instead of idobenzene under usual experimental conditions (2 mmol of **1a**, 2 mmol of PhCOCl, in 5 mL of Et_3N, at 100 °C, for 4-24 h, under N_2) in order to verify if the cyclization could be carried out without carbon monoxide. As a matter of fact Sonogashira reactions of acyl chloride are well known in the literature[25]. Unfortunately, already after 4 hour, almost a complete consumption of the alcohol was observed in the ^{1}H-NMR spectrum of the crude product together with the formation of polymeric material. The obtained results could be probably ascribed to the interaction between the OH moiety of **1a** and the benzoylchloride which can generate esters derivatives that can undergo polycondensation processes.

Conclusion

In conclusion, we have developed an atom-efficient reaction to obtain acylylidene phtalans through a Pd-catalyzed Sonogashira carbonylative reaction[24], followed by an *in situ* cyclizaton process. The reaction proceeds smoothly with both electron-rich and electron-deficient aryl iodides, with almost complete chemoselectivity towards isobenzofuran products. The stereoselectivity of the cyclization step depends mainly on the structure of the benzylalcohol employed. Indeed, when 2-(ethynylphenyl)methanol **1a** was reacted with iodoarenes, carbonylmethylene isobenzofurans **(*Z*)-3** were obtained as major

products together with small amounts of the corresponding *E*-isomers. On the contrary, the reactions performed with *tert*-butyl functionalized alcohol **1b** afforded preferentially the ***E***-stereoisomers which can be easily converted into the corresponding *Z* compounds by simple treatment with $CHCl_3/SiO_2$.

Experimental Section

Typical Procedure for the synthesis of acylylidene isobenzofurans 2

A Schlenk tube was charged with alcohol 1**a** or **1b** (2-4 mmol), aryl iodide **2** (2-4 mmol), and Et_3N (5 mL). This solution was introduced by a steel siphon into the autoclave, previously charged with $PdCl_2(PPh_3)_2$ (0.2-0.5 % mol/mol) and placed under vacuum. The reactor was pressurized with CO (2.0 MPa), and the mixture was stirred for 24 h at 100 C. After removing the excess amount of CO (fume hood), the mixture was diluted with CH_2Cl_2, filtered through Celite, and the solvent was removed under vacuum. The crude product was purified by column chromatography (SiO_2, $CHCl_3$).

Supporting Information: Detailed experimental procedures, spectroscopic data, copies of the ^{1}H NMR and ^{13}C NMR spectra

Keywords: Synthetic methods / Cross-coupling / Carbonylation Cyclisation / Isobenzofurans

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[23] Estimated as:

$$\Delta G° = -RT \ln \frac{[(\boldsymbol{Z}) - \mathbf{3}\boldsymbol{f}]}{[(\boldsymbol{E}) - \mathbf{3}\boldsymbol{f}]}$$

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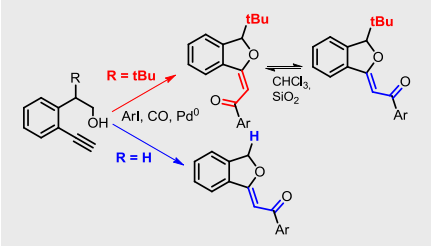
FULL PAPER

A one-step synthesis of a set of functionalised dihydroisobenzofurans was accomplished through copper-free, palladium-catalysed cyclocarbonylative Sonogashira reactions between ethynylbenzyl alcohols and iodoarenes.



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Cyclocarbonylative Sonogashira Reactions of 1-Ethynylbenzyl Alcohols: Synthesis of 1-Carbonylmethylene-1,3-Dihydroisobenzofurans